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Repeated low–dose streptokinase infusions into occluded permanent, central–venous hemodialysis catheters

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Several studies have reported the use of fibrinolytic therapy to re-establish the patency of arterio-venous shunts and fistulas in patients undergoing chronic maintenance hemodialysis [1–7]. In recent years the indwelling Hickman central–venous catheter has been employed as a temporary or permanent access device in patients when more conventional access becomes impossible or when immediate needs for dialysis preclude other alternatives [8]. As with other forms of vascular access, thrombosis and infection remain common problems with these newer devices [9–13].

Streptokinase and urokinase infused directly into the catheter have been used to re-establish flow in patients with occluded single and double lumen catheters placed to administer cancer chemotherapy and parenteral hyperalimentation [11, 12, 14]. Hurtubise et al [11] used low dose instillation of 150 IU of streptokinase directly into the lumen and reported no adverse reactions; however, catheters remained in place for a mean duration of only 29 days and recurrent courses were not mentioned. Zajko et al [12] used continuous infusions of 3000 IU/hour for twelve to 24 hours. Two of his patients had recurrent clotting episodes and developed mild skin reactions with a second exposure to streptokinase. While there is no evidence to indicate that streptokinase antigenicity and bleeding complications are dose related [15], an ideal regimen should deliver the minimum dose required to produce clot lysis and at the same time limit systemic exposure. Guidelines for fibrinolytic therapy with occluded central venous catheters are limited [11, 12, 14]. There is no information about the use of streptokinase in hemodialysis patients with occluded catheters, nor has its repeated use for recurrent loss of patency been reported.

In our experience, using "low–dose" continuous infusions of streptokinase directly into the central venous catheter have been successful in re-establishing catheter patency in a high percent of treated patients with few side effects and an apparent minimal risk of sensitization. We present here the use of this technique in nine patients with multiple recurrent episodes of catheter occlusion over a three year period.

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Methods

Between August 1982 and June 1985, permanent single–lumen (Hickman), central venous catheters were surgically implanted in 51 patients at the University of Maryland Hospital as previously described [8] for the purpose of performing long–term maintenance hemodialysis. Office files and hospital and dialysis records for all patients were reviewed retrospectively to identify multiple episodes of catheter occlusion treated with streptokinase, the dose, duration and method of streptokinase infusion, the outcome of infusion and adverse effects of fibrinolytic therapy.

Catheter occlusion was defined as either the inability to obtain a continuous blood return through the catheter with syringe aspiration or the inability to establish a minimum blood flow rate on hemodialysis of at least 100 ml/minute, whether or not saline could be infused through the catheter. Because proper catheter function is often affected by the patient's position as well as intravascular volume contraction, each patient was carefully repositioned and, when appropriate, was administered 100 to 300 ml of dextran for volume expansion before the catheter was considered to be nonfunctional. Radiographic contrast studies were not performed to confirm a diagnosis of catheter thrombosis.

All patients were admitted to the nephrology ward service of the University of Maryland Hospital for treatment. Routine blood work (complete blood count, white blood cell differential count, PT, PTT and platelet count) was obtained on each patient prior to treatment with streptokinase. Each infusion was continued for a duration of six to 14 hours. The catheter was then tested for patency by either a hemodialysis nurse or an experienced ward nurse by aspirating with a 20 ml syringe. Hemodialysis was initiated immediately if patency was re-established; otherwise the infusion was continued for another 12 hours and the procedure repeated. When catheter patency could not be reestablished after 48 hours of infusion, the treatment was considered to be unsuccessful and the access replaced.

Streptokinase was administered with an intravenous infusion pump in 5% dextrose solution delivered through the catheter at a rate of 1000 to 2000 IU in 10 ml/hr. Two patients had two clotting episodes each in which a bolus injection of 1000 to 2000 IU of streptokinase was administered prior to the i.v. infusion. No other thrombolytic procedures were performed concomi-

Table 1. Dosing parameters for 9 patients with multiple episodes of central venous catheter thrombosis

Patient	No. of clotting episodes	Average dose/ exposure $\times 10^3$ IU	Range $\times 10^3$ IU	Cumulative dose/patient $\times 10^3$ IU	Mean duration of exposure *hours*	Range *hours*
B.L.	6	20	12–60	120	18	12–48
C.G.[a]	4	15	12–24	60	12	12
P.N.[a]	3	11	10–12	33	8.3	6–12
A.K.[a]	2	18	12–24	36	18	23–24
L.B.[a,b]	2	12	12	24	12	12
F.B.[a,c]	4	23.5	12–48	94	20.5	12–36
C.T.	2	12.5	12–13	25	11.5	11–12
C.M.[a]	2	18	12–24	36	12	12
V.F.	3	21	15–24	63	17	12–24
Mean ± SD	3.1 ± 1.4	16.8 ± 5.6	—	54.6 ± 34.0	14.4 ± 4.1	—
Range	2–6	11–23.5	—	24–120	6–48	—

[a] Tested for anti-streptokinase antibody
[b] Developed fever at end of second exposure (T_{max} = 101.2)
[c] Patency not re-established after fourth episode of thrombosis

tantly, and anticoagulants were not given routinely unless the patient had been on maintenance therapy prior to catheter occlusion. Coagulation studies were not routinely obtained following the streptokinase infusions.

Routine catheter care between treatments was performed using a standard protocol originally developed by the University of Maryland Cancer Center for catheters used to permit chemotherapy and parenteral hyperalimentation in oncology patients. At the end of dialysis, the catheter is infused with 3 ml of heparin (1000 units/ml) and capped. Every 24 hours between treatments the catheter is aspirated and reinfused with heparin by the patient, a trained family member or a visiting nurse.

Antibody to streptokinase was tested by Ouchterlony immunodiffusion in six of the nine patients after receiving multiple infusions for recurrent thrombosis. Serum for antibody was obtained two to 11 months after the last occlusive episode in five patients. In the sixth patient (L.B., Table 1), serum was obtained four weeks after the first episode and 24 hours after the second at the time of a temperature elevation.

Results

Between August 1982 and June 1985, catheter occlusion occurred in 25.5% (13 patients) of all patients with permanently implanted central venous catheters. Nine patients had more than one episode (Table 1) with a mean of 3.1 episodes/patient. The mean dose of streptokinase administered per episode was 16,800 IU/patient (range 10 to 60,000) and the mean cumulative dose of streptokinase was 54,555 IU/patient (range 24 to 120,000). The mean duration of infusion for each episode was 15 hours (range 6 to 48).

The mean duration between episodes of catheter occlusion was 4.2 ± 5.9 months (range 22 days to 14 months), and the mean duration from the initial insertion of the catheter to the first episode was 5.2 ± 8.9 months (range 15 days to 28 months) for the 13 catheters inserted in these nine patients.

Hemodialysis was successfully reinstituted in 27 of 28 episodes (96.4%) following streptokinase infusion, and all patients achieved blood flow rates of at least 200 ml/min on dialysis. One patient (L.B.) developed a fever to 101.2 without another source following his second exposure to streptokinase (Table 1), however no other adverse reactions were observed. No patients developed clinically–obvious bleeding disorders or pulmonary emboli, and skin rashes were not seen. Antibody to streptokinase was not detected in the plasma of any of six patients tested after their last exposure to streptokinase.

Discussion

Bleeding, fever and allergic reactions are the most common complications following fibrinolytic therapy [11, 15]. Fever has been reported in up to 25% of patients receiving streptokinase and minor allergic reactions including skin rashes, in 6% [15]. Although reports of anaphylaxis are rare, pretreatment with hydrocortisone has been recommended to avoid potential problems [15–17]. Sharma et al advise that repeat applications be deferred for six to 12 months after an initial course because of its antigenicity [15].

Permanent central venous catheters are being employed more frequently as long–term vascular access for hemodialysis, particularly in individuals where multiple conventional accesses have failed. Loss of function from catheter occlusion is a common problem with these devices and occurred in over 25% of our patients over a 27 month period. This rate is similar to that reported for catheters placed for cancer chemotherapy [11–13] and parenteral hyperalimentation [14].

No attempt was made radiographically to conclusively establish the presence of total or partial catheter thrombosis. The diagnosis was made clinically in each case after conventional maneuvers used to restore blood flow failed. Indeed, angiography may be of limited value in this setting because of the well reported development of fibrin sheaths around chronic indwelling catheters [10].

Recurrent episodes of catheter occlusion occurred in nine patients (17.6%) with a mean interval of 4.2 months between episodes. In these patients, low doses of streptokinase infused at a rate of 1000 to 2000 IU/hour over periods ranging from six to 48 hours were effective in restoring catheter patency in over 96% of cases. These doses were well tolerated with no clinically–apparent bleeding complications or pulmonary emboli observed. Fever occurred in only one case and no skin rashes developed. In our limited experience using pharmacologic fibrinolytic therapy with subclavian catheters and a much more extensive, fourteen year experience using balloon catheters to

declot arteriovenous hemodialysis cannulae, no patient has developed overt pulmonary embolism, although we accept that subclinical embolization is likely a not infrequent occurrence. Based upon this experience, we do not feel that routine evaluation for subclinical embolic phenomena is necessary or indicated.

When tested by immunodiffusion, anti-streptokinase antibody was not detected in any of six patients receiving a maximum cumulative dose of 94,000 IU, including the one patient who developed a febrile reaction after his second exposure to streptokinase.

Each of the patients reported here was hospitalized to monitor therapy. Because of these encouraging results, it may be possible to administer streptokinase infusions in an outpatient setting using larger doses over a shorter interval to avoid the cost of overnight hospital stays. We are currently evaluating such a protocol.

We conclude that repeated applications of streptokinase in the dose range described here are effective and well tolerated. We do not feel that pretreatment with corticosteroids or routine monitoring of coagulation studies is necessary.

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